ORIGINAL ARTICLE

ASSOCIATION OF COMMUNITY-ACQUIRED PNEUMONIA (CAP) WITH INHALED CORTICOSTEROIDS (ICS) AMONG PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Shahzad Alam Khan, Nasir Jamal Khan, Faisal Ramzan

Nishtar Medical University, Multan Pakistan

ABSTRACT

Background: Chronic obstructive pulmonary disease has a significant morbidity burden and adversely affects patient quality of life. According to research, inhaling steroids may raise the chance of developing community-acquired pneumonia (CAP). Since no research had been done in our local community, this study was conducted to determine the relationship between pneumonia and COPD patients. To determine the association of community-acquired pneumonia with inhaled corticosteroids among patients with chronic obstructive pulmonary disease (COPD).

Material and Methods: In a cross-sectional study carried out between October 15, 2020, to April 14, 2022 (18 months) at Nishtar Hospital Multan, 300 COPD patients from the Department of Medicine and Pulmonology were selected after permission from concerned authorities and the Institutional Review Board (IRB). Once registered, all patients underwent clinical examination and chest X-Ray to diagnose pneumonia.

Results: Out of these 300 research cases, our study's patients had an average age of 56.63 ±3.4 years. Out of them, 190 (63.3%) were male patients and 110(27.7%) were female. One hundred and fifty-five (51%) were from metropolitan regions, while 145 (48.3%) were from rural areas. 123 (41.0 percent) of the subjects had diabetes, and 117 (39%) had hypertension. Of these 300 study cases, 200 (66.6 %) were smokers, while dyslipidemia was noted in 136 (45.3 %). Among 300 patients, 247 (82.3%) were on ICS. Community-acquired pneumonia was noted in 43 cases (14.3%). There was a statistically significant association between ICS usage and CAP ($P<0.05$). Post-stratification, CAP had a significant association (p-value ≤ 0.05) with older age (>55 years), urban population, diabetes, smoking, and COPD duration of > 12 months.

Conclusion: Our study noted a high CAP prevalence among COPD patients using ICS. Moreover, community-acquired pneumonia in patients with COPD using inhaled corticosteroids was strongly associated with old age, obesity, DM, smoking, and a long course of the illness. These may be considered as additional risk factors for CAP among ICS using subgroup.

Keywords; Community-acquired pneumonia, CAP, Chronic obstructive pulmonary disease, COPD, Corticosteroids, ICS

BACKGROUND

According to the World Health Organization, COPD is the third leading cause of death globally. Chronic obstructive pulmonary disease (COPD) is responsible for 6% deaths per annum and its mortality distribution remains almost same in all income groups[1]. This illness claims the lives of almost 2.5 million individuals each year. The leading cause of COPD risk is cigarette smoking. Additional important risk factors include occupational dust exposure and hereditary alpha-1 antitrypsin deficiency.[2] Breathing difficulties, a persistent cough that may or may not be productive, and decreased activity tolerance are common symptoms of COPD. These symptoms often worsen while the illness is exacerbated.[3] Use of long-acting β_2 agonists (LABA) in treating COPD in conjunction with ICS is a norm nowadays. Recent clinical trials have shown the efficacy of ICS with LABA in improving lung health and function and reducing the frequency of acute exacerbations (AE) and mortality. However, long-term ICS use has shown an increase in the risk of CAP in COPD patients.[4]

Data published so far shows that the risk of CAP varies with the type of ICS and dose of ICS [5]. It has been observed that pneumonia in patients with COPD has poor outcomes in terms of severity, hospitalization, and complications when compared with patients without COPD.[6] COPD often co-exists with other diseases like bronchiectasis, CVD, chronic kidney disease,

Correspondence: Dr. Shahzad Khan, Assistant Professor, Nishtar Medical University, Multan Pakistan

Email: shahzadalam177735@gmail.com

This article can be cited as: Khan SA, Khan NJ, Ramzan F. Association of community-acquired pneumonia (CAP) with inhaled corticosteroids (ICS) among patients with chronic obstructive pulmonary disease. Infect Dis J Pak. 2023; 32(3): 99-104.

Receiving date: **08 Feb 2023** Acceptance Date: **27 Jun 2023**
Revision date: **20 Apr 2023** Publication Date: **30 Sep 2023**

dyslipidemia, diabetes, hypertension, and lung cancer and may have a significant impact on overall prognosis [7]. A systemic review done in Spain by Miravitlles M *et al*[8] revealed that COPD patients receiving corticosteroids have 41% higher chances of developing pneumonia.

This research assisted in determining the prevalence of CAP among COPD patients receiving ICS in our local population, as we lacked such study in our local population. It gave baseline information regarding our population and identified the problem's current magnitude. Moreover, recent data supports that inhaled ICS-related pneumonia is less severe in lethality; our study would provide grounds for further research once a positive relationship between these two variables was established. And it would help clinicians to anticipate CAP and manage it timely to decrease disease morbidity and mortality. So, we aimed to determine the association between community-acquired pneumonia (CAP) with inhaled corticosteroids among patients with chronic obstructive pulmonary disease (COPD).

MATERIAL AND METHODS

From the 15th of October 2020 to the 14th of April 2022 (18 months), a cross-sectional study was carried out in the medical and pulmonology department of the Nishtar Hospital in Multan. The institutional review board granted ethical permission on 02-10-2020 vide order 12351. Each individual provided written informed consent before being included in the research.

A total of 300 patients of either gender, between the ages of 30-70 years, diagnosed with COPD with no history of hospitalization in the previous 30 days, disease duration (COPD) for more than six months, taking corticosteroids for six months were enrolled in the study by using a non-probability consecutive sampling technique. Subjects having congenital heart disease, ischemic heart disease, cardiomyopathy, bronchial asthma, bronchiectasis or restrictive lung disease, or occupational exposure to asbestos, silica, or coal based on history were ruled out from the study. COPD was labeled in those with either FEV1/FVC <70% and <15% reversibility of FEV1 after β2-agonist use done six months back or with already established diagnosis based on history and medical records along with taking inhaled corticosteroid therapy as prescribed by the clinician for more than six months. CAP was diagnosed if the patient had a fever ≥101˚F, cough, difficulty breathing, and tachypnea (24 breaths/minute) for more than three days, along with radiological findings such as air space opacity, lobar consolidation, or interstitial opacities. Patients smoking at least ten cigarettes per day for more than two years were labeled as smokers.

The patient's biodata and demographic information were recorded using a pre-designed questionnaire. Age, gender, residence status, socioeconomic position, diabetes, hypertension, obesity, dyslipidemia, smoking history, and length of disease were among the demographics gathered and recorded. Once registered, all patients underwent clinical examination and chest x–rays to diagnose pneumonia.

Data were analyzed using SPSS v.24. For patient age and disease duration, the mean and standard deviation were determined. Frequencies, along with percentages, were recorded for gender, obesity, dyslipidemia, residential status, monthly family income, age groups, and the presence of pneumonia, smoking, diabetes, and hypertension. Chi-square analysis was used to establish an association between CAP and ICS-treated COPD patients. Stratification was done to overcome effect modifiers such as age, gender, smoking, diabetes, obesity, hypertension, disease duration, and residential status. After stratification, the Chi-Square test was applied again. P value $\leq$ 0.05 was considered significant.

RESULTS

A total of 300 COPD patients who met the inclusion criteria were enrolled. Of 300 cases, 190 (63.3 %) were males, while 110 (36.7%) were females. Our study's patients had an average age of 56.63 ±3.4 years. According to the findings of our study, 198(66%) patients were older than 55. Out of 300, 155 (51.7%) belonged to the urban population while 145 (48.3%) lived in rural areas. Regarding socioeconomic status, 188 (62.7%) belonged to poor socioeconomic status, while 112 (37.3%) patients were in the middle-income group. Diabetes was present in 123 (41%), and 117 (39%) were hypertensive. The mean BMI was 25.43 ± 4.15 kg/m^{2,} and 22.0 % of cases were obese. The mean duration of illness was 18.39 ± 7.76 months, and 204 (68.0%) had more than one year of illness. Of these 300 study cases, 200 (66.3%) were smokers, while dyslipidemia was noted in 136 (45.3%) (Table-I).

The total number of COPD patients who were on Inhaled corticosteroids (ICS) was 247 (82.3%), while the patients who developed community-acquired pneumonia were 43 (14.3%). Out of 43, two patients who were not on ICS developed CAP. On chi-square analysis, there was a significant association between ICS and CAP ($p<0.05$) (Table-II)

The frequency of CAP was stratified against gender, age groups, residential status, diabetes, hypertension, obesity, COPD duration, and smoking. CAP had a significant association (p-value ≤ 0.05) with the old age group (>55 years), urban population, diabetes, smoking, and COPD duration of more than 12 months as shown in Table-III.

Table-I: Demographic properties of study population (n=300).

Variables		Frequency	Percentage
Gender	Male	190	**63.3%**
	Females	110	**36.7%**
Residence	Rural	145	**48.3%**
	Urban	155	**51.7%**
Dyslipidemia	Yes	136	**45.3%**
Age Groups	≤55 years	102	**34%**
	>55 years	198	**66%**
Diabetics	Yes	123	**41%**
Hypertensive	Yes	117	**39%**
Smoking	Yes	200	**66.7%**
Socioeconomic	Poor	188	**62.7%**
Status	Average	112	**37.3%**
Obese	Yes	66	**22%**

Table-II: Association between ICS and CAP.

		CAP		Total	
		Yes	No		
ICS USE	No	2	51	53	P- value= **0.016** (<0.05)
	Yes	41	206	247	
Total		43	257	300	

Table-III: Stratification of various factors with CAP in patients using ICS.

VARIABLES		ICS USE		Community-Acquired Pneumonia		Total	P-Value
	GROUPS			Yes	No		
Gender	MALES N=190	ICS	No	2	37	37	0.087
			Yes	25	138	153	
	FEMALES N=110	ICS	No	0	16	16	0.074
			Yes	16	78	94	
Age Group	≤55 years (N=102)	ICS	No	2	10	12	0.853
			Yes	17	73	90	
	>55 years (N=198)	ICS	No	0	41	41	**0.08**
			Yes	24	133	157	
Residence	Rural (N=145)	ICS	No	2	19	21	0.27
			Yes	24	100	124	
	Urban (N=155)	ICS	No	0	32	32	**0.026**
			Yes	17	106	123	
Diabetes	Diabetics (N=123)	ICS	No	2	17	19	**0.022**
			Yes	39	65	104	
	Non-Diabetics	ICS	No	1	33	34	0.625

	(N=177)		Yes	1	142	143	
Hypertension	Hypertensive (N=198)	ICS	No	2	9	11	0.438
			Yes	31	75	106	
	Non-HTN (N=198)	ICS	No	0	42	42	0.076
			Yes	10	131	141	
Obesity	Obese (N=66)	ICS	No	1	27	28	**0.0001**
			Yes	17	21	38	
	Non-Obese (N=234)	ICS	No	1	24	25	0.252
			Yes	24	185	209	
Smoking	Smokers (N=200)	ICS	No	0	31	31	**0.019**
			Yes	26	143	169	
	Non-Smokers (N=100)	ICS	No	2	20	22	0.263
			Yes	15	63	78	
Disease Duration	≤12 Months (N=96)	ICS	No	2	15	17	0.416
			Yes	16	63	79	
	>12 months (N=204)	ICS	No	0	36	36	**0.013**
			Yes	25	143	168	

DISCUSSION

Chronic obstructive pulmonary disease is a common ailment that may be prevented and managed according to the global strategy for treating, managing, and preventing it.[9] It may be identified by a persistent airflow limitation that is often progressive and associated with an aggravated chronic inflammatory reaction to hazardous particles or gases in the lungs or airways. It is proved in multiple clinical trials, that a fixed-dose combination of an ICS and long-acting β_2-agonist (LABA) used in the treatment of COPD, not only decreases the frequency of COPD exacerbations[10] by about 25% but also slows down disease progression[11] and prognosis of disease also improves.[12] Use of this combined therapy not only has better bronchodilator properties but is even better at preventing exacerbation when compared to bronchodilator therapy alone.[13.] Variations in results in terms of exacerbation frequency and prognosis have been noted with various ICSs.

However, it has been identified that ICS use in COPD is a potential risk factor for various adverse effects including a higher risk of pneumonia, tuberculosis, atypical mycobacterial infections, bone fracture resulting from osteoporosis, poor diabetic control, and local effects like oral thrush, hoarseness of voice, cough. Rabe KF *et al*[14] have recorded higher CAP frequency among COPD patients using ICS. The chances of CAP were more likely with lipophilic potent ICSs such as fluticasone and less likely with beclomethasone and budesonide.[15]

In our study, we had 190 (63.3%) male patients, and 110 (36.7%) female patients. Most studies[16,17,18] also show male preponderance but a study from Peshawar revealed otherwise.[19] Hence it is important to study more local data to generate population-based evidence.

Our study population had an average age of 56.63 ±3.4 years. Our study showed that 198 patients, or 58.7%, were older than 55. Studies conducted by Jamil M[18] and Iftikhar *et al*[20] also reported a higher frequency of COPD among patients above 50 years.

Of the 300 study cases, 145 (48.3%) were from rural areas, whereas 155 (51.7%) belonged to metropolitan areas. One hundred eighty-eight people (62.7%) had low socioeconomic levels, while 112 (37.3%) had a modest income. In 123 (41 percent) of the research participants, diabetes was present. 117 (39 percent) of the study patients had hypertension. The average BMI of the research participants was 25.43 ± 4.15 kg/m2, and 66 (22.0 percent) of them were obese. Research by Mahishale *et al*[21] also found a diabetes prevalence of 21.24% among COPD patients, which is slightly less than our study's findings. It may be due to higher prevalence of diabetes in our population.

The average disease duration was 18.39 ± 7.76 months, and 204 (68.0%) had more than one year of illness. 200 (66.6%) of the 300 research participants had a smoking history, and 136 (136%) had dyslipidemia (45.3 percent). According to research by Ahmad *et al*[18] and Iftikhar *et al*[21] from Peshawar, 37.5% and 38% of participants had ever smoked respectively, which is inconsistent with the findings of our investigation. It may be due to other factors for COPD like bidi chewing and naswar use.

Community-acquired pneumonia was noted in 43 (14.3%) patients. According to Lin *et al*[22] study, which was carried out in Taiwan, 19.5% of cases of CAP in COPD patients occurred with ICS use, which is consistent with our study's findings. Ritchie A *et al*.[23] conducted a population-based case-control study in the UK and found that ICS use was associated with 26% increased risks of CAP in COPD patients. They also observed that recent ICS use was more strongly related to CAP.

Lin SH *et al*[24] has identified high prevalence of CAP among elderly age group and diabetics. Our results are congruent with these findings. However, Lin SH *et al*. didn't establish this association of advanced age and diabetes with CAP in ICS using subgroup but we studied it in ICS using subgroup and established association of these two variables with CAP in ICS subgroup which is a peculiar feature of our study. Mkorombindo T *et al*[25] noticed that CAP was more frequent in those ICS patients who had low BMI and advanced age. Our results are partially consistent with these findings because we also found high prevalence of CAP in ICS subgroups with advanced age but we found that it was more common among obese patients. This discrepancy may again be attributed to high prevalence of diabetes among obese patients.

CONCLUSION

Patients with the chronic obstructive pulmonary disease had a significant frequency of community-acquired pneumonia, according to our research. Significant association have been shown between community-acquired pneumonia and ICS use in the older age group (>55 years), urban population, diabetics, smokers, and COPD duration of more than 12 months. All medical professionals caring for such individuals should consider them at risk for developing community-acquired pneumonia. Early detection and treatment of community-acquired pneumonia may enhance clinical outcomes and lower disease-related morbidity.

LIMITATION OF STUDY

As the study was conducted only in a tertiary care center so it may not give a true picture of disease prevalence. Moreover, the frequency of CAP was not determined separately in different types of ICS so we can't tell with surety which type of ICS and what dose of ICS is notorious for causing CAP. Further studies may be required to address other aspects of ICS-related CAP among COPD patients which have not been covered in our study. Additional work is required to identify risk factors for increased incidence of CAP in ICS using subgroup.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

AUTHOR CONTRIBUTION

Shahzad Alam Khan: Conception or design of the work, literature search, questionnaire design, data collection

Faisal Ramzan: Literature search, Data analysis, data interpretation, drafting

Nasir Jamal Khan: Data collection and drafting, literature search

REFERENCES

1. World Health Organization. The top 10 causes of death. 2018. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
2. Javaid MA, Amir M, Faheem M. Chronic Obstructive Pulmonary Disease and pulmonary rehabilitation: Awareness among the patients. Pak Armed Force Med J 2020; 70: 721–6.
3. Pal A, Howarth TP, Rissel C, Messenger R, Issac S, Ford L, *et al*. COPD disease knowledge, self-awareness and reasons for hospital presentations among a predominately Indigenous Australian cohort: a study to explore preventable hospitalization. BMJ Open Respir Res 2022; 9: e001295. DOI: doi.org/10.1136/bmjresp-2022-001295.
4. Martinez-Garcia MA, Faner R, Oscullo G, de la Rosa D, Soler-Cataluña JJ, Ballester M, *et al*. Inhaled steroids, circulating eosinophils, chronic airway infection, and pneumonia risk in chronic obstructive pulmonary disease. A network analysis. Am J Respir Crit Care Med 2020; 201: 1078–85. DOI: doi.org/10.1164/rccm.201908-1550OC.
5. Brode SK, Campitelli MA, Kwong JC, Lu H, Marchand-Austin A, Gershon AS, *et al*. The risk of mycobacterial infections associated with inhaled corticosteroid use. Eur Respir J 2017; 50: 1700037. DOI: doi.org/10.1183/13993003.00037-2017

6. Bonnesen B, Baunbæk Egelund G, Vestergaard Jensen A, Andersen S, Trier Petersen P, Rohde G, *et al*. Is chronic obstructive pulmonary disease a risk factor for death in patients with community acquired pneumonia? Infect Dis (Lond) 2019; 51: 340–7. DOI: doi.org/10.1080/23744235.2019.1565416
7. Lisspers K, Larsson K, Janson C, Ställberg B, Tsiligianni I, Gutzwiller FS, *et al*. Gender differences among Swedish COPD patients: results from the ARCTIC, a real-world retrospective cohort study. NPJ Prim Care Respir Med 2019; 29: 45. DOI: doi.org/10.1038/s41533-019-0157-3
8. Miravitlles M, Auladell-Rispau A, Monteagudo M, Vázquez-Niebla JC, Mohammed J, Nuñez A, *et al*. Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of COPD. Eur Respir Rev 2021; 30: 210075. DOI: doi.org/10.1183/16000617.0075-2021.
9. Celli BR, Singh D, Vogelmeier C, Agusti A. New perspectives on chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2022; 17: 2127–36. DOI: doi.org/10.2147/COPD.S365771.
10. MacLeod M, Papi A, Contoli M, Beghé B, Celli BR, Wedzicha JA, *et al*. Chronic obstructive pulmonary disease exacerbation fundamentals: Diagnosis, treatment, prevention and disease impact. Respirology 2021; 26: 532–51. DOI: doi.org/10.1111/resp.14041
11. Avdeev S, Aisanov Z, Arkhipov V, Belevskiy A, Leshchenko I, Ovcharenko S, *et al*. Withdrawal of inhaled corticosteroids in COPD patients: rationale and algorithms. Int J Chron Obstruct Pulmon Dis 2019; 14: 1267–80. DOI: doi.org/10.2147/COPD.S207775
12. Fu Y, Chapman EJ, Boland AC, Bennett MI. Evidence-based management approaches for patients with severe chronic obstructive pulmonary disease (COPD): A practice review. Palliat Med 2022; 36: 770–82. DOI: doi.org/10.1177/02692163221079697
13. Williams DM. Clinical pharmacology of corticosteroids. Respir Care 2018; 63: 655–70. DOI: doi.org/10.4187/respcare.06314
14. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, *et al*. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. N Engl J Med 2020; 383: 35–48. DOI: doi.org/10.1056/NEJMoa1916046
15. Lee J-H, Park YH, Kang DR, Lee SJ, Lee MK, Kim S-H, *et al*. Risk of pneumonia associated with inhaled corticosteroid in patients with chronic obstructive pulmonary disease: A Korean population-based study. Int J Chron Obstruct Pulmon Dis 2020; 15:3397–406. DOI: doi.org/10.2147/COPD.S286149
16. Alqahtani JS. Prevalence, incidence, morbidity and mortality rates of COPD in Saudi Arabia: Trends in burden of COPD from 1990 to 2019. PLoS One 2022;17: e0268772. DOI: doi.org/10.1371/journal.pone.0268772
17. Soriano JB, Alfageme I, Miravitlles M, de Lucas P, Soler-Cataluña JJ, García-Río F, *et al*. Prevalence and determinants of COPD in Spain: EPISCAN II. Arch Bronconeumol 2021; 57: 61–9. DOI: doi.org/10.1016/j.arbr.2020.07.017
18. Jamil M, Siddique MU, Shah MH, Mahmood RK, Ahmad N, Alam M, *et al*. Frequency of hypomagnesemia in patients with chronic obstructive pulmonary disease (COPD). Pak J Medical & Health Sci. 2023; 17. DOI: doi.org/10.53350/pjmhs2023171251
19. Ahmad H, Zaman M. An audit of the management of patients admitted with acute exacerbation of COPD at a tertiary care hospital. Pak J Chest Med 2015; 21: 68–75.
20. Iftikhar B, Khan MH, Hussain H, Iqbal M, Jadoon GS. Relationship between silica dust exposure and chronic obstructive pulmonary disease in workers of dust generating industries of district Peshawar. Gomal J Med Sci 2009; 7: 46–50.
21. Mahishale V, Mahishale A, Patil B, Sindhuri A, Eti A. Screening for diabetes mellitus in patients with chronic obstructive pulmonary disease in tertiary care hospital in India. Niger Med J 2015; 56: 122–5. DOI: doi.org/10.4103/0300-1652.150699.
22. Lin S-H, Perng D-W, Chen C-P, Chai W-H, Yeh C-S, Kor C-T, *et al*. Increased risk of community-acquired pneumonia in COPD patients with comorbid cardiovascular disease. Int J Chron Obstruct Pulmon Dis 2016; 11: 3051–8. DOI: doi.org/10.2147/COPD.S115137.
23. Ritchie AI, Singanayagam A, Mitchell S, Wedzicha J, Shah A, Bloom C. S113 The risk of pneumonia in COPD patients with concomitant bronchiectasis using inhaled corticosteroids: a UK case-control study. 'The Winter Soldier' – Pneumonia epidemiology and impact, BMJ Publishing Group Ltd and British Thoracic Society; 2022. DOI: doi.org/10.1136/thorax-2022-btsabstracts.119.
24. Lin SH, Perng DW, Chen CP, Chai WH, Yeh CS, Kor CT, Cheng SL, Chen JJ, Lin CH. Increased risk of community-acquired pneumonia in COPD patients with comorbid cardiovascular disease. International journal of chronic obstructive pulmonary disease. 2016 Dec 5:3051-8. DOI: doi.org/10.2147/COPD.S115137
25. Mkorombindo T, Dransfield MT. Inhaled corticosteroids in chronic obstructive pulmonary disease: benefits and risks. Clinics in chest medicine. 2020 Sep 1;41(3):475-84. DOI: 10.1016/j.ccm.2020.05.006